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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/061,417	04/16/98	OLSON E	UTSD:548

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STEVEN L. HIGHLANDER
FULBRIGHT AND JAWORSKI
P O BOX 4433
600 CONGRESS AVE, SUITE 78701
AUSTIN, TX 78701

EXAMINER	
DAVIS,M	
ART UNIT	**PAPER NUMBER**
1642	15

DATE MAILED: 07/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/061,417	Olson et al
Examiner	**Art Unit**
Minh-Tam Davis	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 29, 2000*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above, claim(s) *2, 3, 5-8, and 10-40* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 4, and 9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7 sheets*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

Applicant's election of group V, claims 1, 4, 9, a small molecule inhibitor, in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 1, 4 and 9, a small molecule inhibitor, are examined in the instant application.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1, 4, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1, 4, and 9 are indefinite, because claim 1 lacks essential steps, i.e. a step reciting how the function of NF-AT3 is inhibited, and a step correlating the result with the preamble.

2. Claims 4, 9 are indefinite, because it is not clear in claim 4 where the location of NF-AT3 is. Is it in a cell culture medium? This rejection could be obviated by replacing contacting "NF-AT3" with contacting "said cardiomyocyte cell".

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1, 4, 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 1, 4, 9 are drawn to a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and inactivates NF-AT3, wherein said agent is a small molecule inhibitor.

The specification contemplates the use of a single chain antibody that could inhibit the binding of NF-AT3 to calcineurin (p.28-29). The specification also contemplates the use of a mimetic of beta-turns within GATA4, that binds to NF-AT3 in a manner analogous to the transcriptional factor GATA4, and specifically inhibits NF-AT3 binding to GATA4 (p.29).

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The claims, as written, however, encompass a method for treating hypertrophy of a cardiomyocyte cell, comprising contacting NF-AT3 with any small inhibitor molecules having any structure or composition.

The instant disclosure of a single species of scFv of an antibody, does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. The instant specification fails to provide sufficient descriptive information, such as definitive

strutural features of the claimed genus of small molecule inhibitors. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, although molecular modeling is known in the art, the structure of the claimed small molecule inhibitors is unpredictable, especially in view of the fact that the configuration of the second zinc finger of GATA4, a site for the binding of GATA4 to NF-AT3 (specification, p.74, second paragraph) is not disclosed in the specification, nor is it known in the art at the time the invention was made. The prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the small molecules encompassed and no identifying characteristic or property of the instant small molecules is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a single chain of an antibody is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Thus, only a method for treating hypertrophy in a cardiomyocyte cell, comprising exposing to said cell sFv of an antibody that inhibits the binding of NF-AT3 to

calcineurin, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1, 4, and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 4, 9 are drawn to a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and inactivates NF-AT3, wherein said agent is a small molecule inhibitor.

The specification speculates that cardiac hypertrophy is caused by activated NF-AT3, which is interacting with GATA4 in cardiomyocyte cells, resulting in up-regulation of cardiac hypertrophic genes, and thus cardiac hypertrophy could be treated if the activity of NF-AT3 is inhibited. The specification discloses the following hypothetical chains of reactions: Hypertrophic stimuli such as AngII and PE, which lead to an elevation of intracellular calcium, result in activation of calcineurin. Calcineurin would dephosphorylate NF-AT3 in the cytoplasm of cardiomyocytes, enabling its translocation to the nucleus, where it can interact with GATA4, resulting in up-regulation of cardiac hypertrophic genes, such as beta-naturietic peptide (BNP), responsible for hypertrophy (p.13, first paragraph and figure 8).The specification discloses that

cardiac hypertrophy has been known to be associated with elevation of intracellular calcium (p.9, last paragraph). The specification also discloses that calcineurin, which is a phosphatase, is activated by a sustained calcium plateau, and is insensitive to transient calcium fluxes as occur in response to cardiomyocyte contraction (p.11, last paragraph). The specification further discloses that NF-AT3 is a member of a multigene family comprising NF-ATc, NF-ATp, NF-AT3 and Nf-AT4, and that NF-AT3 is expressed in a variety of tissues including the heart. The reference by Hoey et al, 1995 is referred to for the NF-AT3 tissue location information (specification, p.12, second paragraph). In addition, the specification discloses that in T cells, changes in gene expression in response to calcineurin are mediated by members of the NF-AT family of transcriptional factor, which translocate into the nucleus following dephosphorylation by calcineurin (p. 13, second paragraph). In example 2 in the specification, from mouse embryo cDNA, numerous GATA4-interacting factors, including NF-AT3, are identified. In example 4, in transfected cardiomyocytes, BNP promoter is activated in the presence of GATA4, NF-AT3 and calcineurin. In example 4, page 75, last paragraph, bridging page 76, antibodies specific for NF-AT3 are able to eliminate complexes formed between BNP promoter and cardiac protein extracts. In example 8, transgenic mice expressing in the hearts mutant NF-AT3, which is constituvely, i.e. continuously, activated, show extensive cardiac hypertrophy.

It is noted however that there is no disclosure of actual treatment of said hypertrophic transgenic mice with any compound that inhibits NF-AT3, including the claimed small molecule inhibitors of NF-AT3, nor treatment of cardiomyocyte cells, which are exposed to hypertrophic

stimuli such as AngII and PE, with any compound that inhibits NF-AT3, including the claimed small molecule inhibitors.

One could not extrapolate the teaching of the specification to the claims. It is not clear whether NFAT3 actually expresses as protein in heart muscle in nature. Hoey T et al, 1996, WO 96/26959 teach that different members of NFATs express in different distinct tissue-specific patterns (p.19). Using Northern hybridization, NFAT4, like NFATc, is found to strongly express in skeletal muscle, besides in thymus. NFTA3 however is highly expressed as mRNA in placenta, lung, kidney, testis, and ovary. Further in the reference by Hoey T et al, Immunity, 2: 461-472, as referred in the specification, it is NF-ATc, not NFTA3, that is found to express as mRNA in skeletal muscle (p.469, second column, paragraph before last). Thus there is no evidence as claimed in the specification that NFTA3 mRNA is expressed in the heart muscle. Further, even if NFTA3 mRNA is expressed in the heart muscle, it is unpredictable that said NFTA3 mRNA would be translated into protein in heart muscle. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that

ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Moreover, eventhough the specification discloses that antibodies specific for NF-AT3 are able to eliminate complexes formed between BNP promoter and cardiac protein extracts, the specification does not disclose whether non-specific antibodies would also eliminate complexes formed between BNP promoter and cardiac protein extracts. It is unpredictable that the proteins which are complexed with BNP promoter are actually NF-AT3, unless tested, because the specification has not shown that the claimed antibodies used in the test would not also bind to other proteins present in cardiac protein extracts.

For the above reasons, one of skill in the art would not be able to predict if NFTA3 would in fact be expressed as protein in heart muscles.

In addition, even if NFTA3 is expressed as protein in heart muscle, one cannot predict that NF-AT3 actually interacts with GATA4 in nature, in cardiomyocyte cells *in vivo*, because of the following reasons: The interaction between NF-AT3 and GATA4 in example 2 is only from mouse embryo libraries, which are not cardiomyocyte cells, and one cannot predict that there is the same interaction between NF-AT3 and GATA4 in cardiomyocyte cells . Further, although BNP promoter is up-regulated in the presence of GATA4, NF-AT3 and calcineurin in cardiomyocyte cells, as disclosed in example 4, the cardiomyocyte cells are however transfected with GATA4, NF-AT3, the artifial condition of overexpression and overabundance of which could effect the distribution and thus forced interaction between GATA4 and NF-AT3. Further, the transfected calcineurin is in a mutant form, which is constitutively, i.e. continously, active. Thus the conditions of the transfected cells would not be even remotely similar conditions as in hypertrophic cardiomyocyte cells *in vivo*. Further, one could not apply *in vitro* conditions to *in vivo* conditions because characteristics of cultured cell lines generally differ significantly from the characteristics of a primary cell. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant

in vitro but may not be truly representative of the tissue from which the cells were derived. Thum T et al, 2001, Transplantation, 71(4): 543-52, teach that the levels of expression of target genes of GATA-4 in cells in cultures are different as compared to those from freshly isolated cells. Similarly, the transgenic mice having cardiac hypertrophy, wherein a transfected mutant NF-AT3, which is continously activated, and expressed in the hearts, do not represent a model for cardiac hypertrophy for human. Applicant has not shown that NF-AT3 is continously activated in the hearts of patients having cardiac hypertrophy, and is responsible for up-regulation of cardiac hypertrophic genes via interaction with GATA4 *in vivo* in patients with cardiac hypertrophy.

The scope of the claims however encompasses a method for treating cardiac hypertrophy, which does not read on treating transfected cells or transgenic mice carrrying mutant NF-AT3, which is continously activated, and expressed in the hearts. It is clear that the disclosure in the specification is not commensurate in scope with the claimed invention.

Further, even if NF-AT3 is responsible for up-regulation of cardiac hypertrophic genes *in vivo* in patients with cardiac hypertrophy, the epitope on NF-AT3 where the claimed small molecule inhibitors are supposed to bind to is unpredictable, since the specification does not disclose the structure of the active site of NF-AT3. There is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the

specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by the claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column).

Moreover, it is unpredictable that the claimed small molecule inhibitors would be effective in treating cardiac hypertrophy. It is well known in the art, and as disclosed in the specification, that NFATs, or nuclear factors of activated T-cells, exist in the cytoplasm and in the nucleus of T cells when activated. In other words, NF-AT 3 is not a membrane antigen. It is also well known in the art that antibodies would enter into a cell only via binding to a cell surface antigen. It is not clear how the claimed small molecule inhibitors, including single chain antibodies specific for NF-AT3, could travel across the cell membrane of cardiomyocytes and are targeted to NF-AT3. Further, an anti-NF-AT3 agent must accomplish several tasks to be effective. It must be delivered into the circulation and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addtion variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy.

The claimed small molecules may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the small molecules. In addition, the claimed small molecules may not otherwise reach the targert because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the claimed small molecules has no effect, circulation into the target area may be insufficient to carry the claimed small molecules and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which woul allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

July 5, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600